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A Brief Overview on Osteoarthritis Pathogenesis Management and Treatment

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ABSTRACT

Degradation of cartilage, remodelling of subchondral bone, and synovial inflammation are the hallmarks of osteoarthritis (OA), a degenerative illness. Obesity, mechanical strain, and age are linked to the illness. However, the production of metalloprotexfcxinases, which are involved in the destruction of cartilage, is regulated by a number of pro-inflammatory immunological mediators. In addition, OA susceptibility is influenced by hereditary factors. The expression of genes linked to OA may be regulated by epigenetic processes, according to recent research. The mechanism of OA pathogenesis will be discussed in this review, along with an overview of the most recent research on the contribution of genetics and epigenetics to this process.

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INTRODUCTION

With over 500 million cases reported in 2019, osteoarthritis (OA) is the most common joint disease in humans. The condition is becoming more and more common as a result of ageing, obesity, and traumas. Articular cartilage (AC) gradually degrades in osteoarthritis (OA), causing harm to the bone, synovium, and ligaments.(1)

A variety of metabolic, mechanical, and inflammatory variables are involved in the diverse pathophysiology of osteoarthritis. A structural defect results from an imbalance between the mechanisms that destroy and restore joint tissues. Though it can occur in any synovial joint, OA most commonly affects the hands, knees, and hips.(2)

Osteoarthritis (OA) is characterised by pain, stiffness, and limited movement. Bouchard and Heberden nodes, which are swellings of the afflicted joints, are another sign of osteoarthritis (OA) in the hand. Other than the standard risk factors for osteoarthritis (OA) such as obesity, older age, mechanical stress, etc., newer research focuses on looking for a genetic predisposition.(3)

Risk factors

The OA is associated with several established risk factors, such as advanced age, obesity, hereditary susceptibility, acute trauma and chronic overload, hormone profile, gender, and metabolic syndrome.(4) It should be highlighted, nevertheless, that OA is not a necessary side effect of these elements. Furthermore, it's possible that many risk factors contribute to the aetiology of osteoarthritis. For instance, among senior citizens with OA with an anterior cruciate ligament injury progresses more quickly in older persons. (5,6)

a) Aging

The main risk factor for OA is ageing, which is defined as the gradual loss of tissue and organ function over time.(7) The Framingham Osteoarthritis Study has established that the frequency of radiographically evident OA, i.e., joint space narrowing, increases with each decade, beginning at 12.9% in people 30–40 years of age and increasing to 43.7% in people over the age of 80.(8,9) The accumulation of random unrepaired molecular damage to DNA, proteins, and lipids over time has been proposed as one of the mechanisms of cellular ageing. This process eventually results in cellular defects and tissue dysfunction, which in turn causes increased frailty and age-related diseases.(10) Reactive oxygen and nitrogen species

generated by mitochondria and cellular stress responses, respectively, are the main causes of this damage. The accumulation of somatic mutations and DNA damage, telomere shortening, protein and lipid degradation, and mitochondrial dysfunction are the immediate effects of these reactive oxygen species (ROS).(10)

b) Trauma

Post-traumatic osteoarthritis (PTOA) is frequently brought on by joint instability or intraarticular fractures resulting from severe injury. Unusual loading vectors and elevated contact stresses brought on by joint damage are known to harm articular cartilage.(11,12)

About 12% of all OA is caused by PTOA, with weight-bearing joints being the most vulnerable. For instance, trauma to the knee components, such as meniscal resection and anterior cruciate ligament (ACL) tears, causes radiographic OA to grow earlier in life.(13,14)

According to estimates, 21% of individuals with ACL transection injuries get PTOA; this number rises to 48% in patients who also have concurrent meniscal injuries. In contrast, post-traumatic origin accounts for 70–80% of instances with radiographic ankle OA, and the majority of patients are younger than those with primary ankle OA.(15,16)

Trauma to the articular cartilage mostly results in the early death of cells by necrosis and apoptosis, followed by an increase in reactive oxygen species (ROS) and nitric oxide synthases (NOS) production.(17)

c) Obesity

Body Mass Index (BMI) more than 30 kg/m2 is considered obesity. It has become an epidemic-scale global issue. Walking generates a force on the knee that is three to six times more than one's body weight, therefore carrying more weight increases the pressures placed on the joints [51]. According to a recent meta-analysis, people who are overweight or obese had odds ratios (OR) of 1.98 (95% CI 1.57e2.20) and 2.66 (95% CI 2.15e3.28) for developing knee OA, respectively.(18) On the other hand, losing weight dramatically reduced the chance of developing knee OA. A reduction in body mass index of two units or more (equivalent to a weight loss of around 5.1 kg) over the ten years preceding the specified test reduced the risks of getting osteoarthritis by more than fifty percent, according a Framingham research conducted on women.(19)

d) Chronic Mechanical Overloading/Overuse

The constant application of physiologic mechanical loading to chondrocytes is necessary to preserve the homeostatic balance between the catabolic and anabolic processes. This balance is achieved by reducing the activity of matrix-degrading enzymes, enhancing anti-inflammatory signalling, and suppressing proinflammatory cytokines and inflammatory mediators.(20) However, it has been seen that supraphysiological loading tips the scales in favour of catabolic processes that cause OA, subchondral sclerosis, thinning cartilage, and bone marrow lesions beginning.(21,22,23)

Weight-bearing sports activity was linked to a 2-3fold increase in radiologic OA risks in a research involving former top female athletes (24). Long-term hard lifting or prolonged standing at work has been linked to hip OA, according to another workload research (25). It should be highlighted that anatomical location and history significantly influence physiological loading in vivo (26), and the region experiencing more cartilage loss is frequently linked to higher mechanical loading.(27)

e) Genetics

OA is seen as a multifactorial polygenic illness that is impacted by a variety of environmental and genetic variables.(28) Heritance studies using twin pairs and family groups have shown that 37–78% of cases of OA are genetically related (29,30). Mutations in specific genes not only cause OA directly, but they may also dictate the age at which the illness first manifests and the locations of affected joints, as well as the degree and pace of OA development (31). prevalent single-nucleotide polymorphisms (SNPs) with minor allele frequencies (MAF) > 5% and moderate to modest effect sizes (OR: ~1.1–1.3) are the most prevalent representations of known OA-associated variations.(32)

Pathogenesis of Osteoarthritis

The aetiology of OA, a whole-joint disease, is complicated and multifaceted. First off, it is now thought that cartilage degradation is facilitated by the stimulation of inflammatory pathways by mechanical damage, which in turn triggers the production of proteases that break down the extracellular matrix (ECM). These proteases are a part of the secretome of chondrocytes, along with a wide range of other cytokines, growth factors, extracellular matrix (ECM) proteins, and other enzymes . The ECM remodelling that these cartilage-specific cells orchestrate can be either a normal or pathological process. The synovium, a fibrous capsule

that generates synovial fluid, envelops the joint. Synovial inflammation is one of the main characteristics of OA.(33)

Remarkably, new research has begun to shed light on the possible contribution of a dysregulated microbiota to the development of osteoarthritis. When OA patients are compared to healthy controls, there is a considerable change in the abundance of the gut microbiome (bacteriome, mycobiome, and virome). For example, OA patients had greater amounts of Proteobacteria and Actinobacteriota.(34)

As a result, the pathophysiology of OA is a multifaceted process that may include a number of processes, including inflammation, trauma, and dysregulated microbiota. Numerous cells participate in the deterioration of articular cartilage and may create a positive feedback loop, which advances the pathophysiology of osteoarthritis.(35)

Pathological Changes in Osteoarthritis

Pro-inflammatory cytokines induce the continual synthesis of proteases, which leads to severe matrix breakdown in OA. The synthesis of proteases, nitric acid (NA), and eicosanoids (prostaglandins and leukotrienes) in chondrocytes and macrophages is stimulated by the upregulation of interleukin (IL) 1, 6, and 8. Consequently, there is an increase in cell death, an inhibition of matrix production, and stimulation of catabolic pathways. Particularly, the production of metalloproteinases (MMP)-1, 3, and 13 is enhanced by IL-1 and tumour necrosis factor (TNF)-α, which in turn decreases the synthesis of matrix components such type II collagen, aggrecans, and proteoglycans and accelerates the breakdown of cartilage matrix. More specifically, the breakdown of the collagenous framework is caused by the proteases MMP-1 and MMP-13, whereas the breakdown of the proteoglycan is caused by stromelysin (MMP-3) and the aggrecan ADAMT-4. (36)

Additional inflammatory mediator enzymes that are changed in OA include cyclooxygenase-2 and inducible nitric oxide synthase (iNOS). Increased gene expression drives the overexpression of these enzymes. The production of NO by iNOS is what causes cartilage deterioration. It also suppresses the synthesis of collagen and proteoglycans and upregulates MMPs. COX-2 not only prevents the formation of collagen and proteoglycans but also produces prostaglandin E2 (PGE2). PGE2 overproduction causes OA to become more inflammatory, more apoptotic, and to undergo structural alterations [8]. Together, all of these

mechanisms contribute to the onset and advancement of OA. We can target the illness by blocking or changing either of them.(37)

Existing market treatment for osteoarthritis

Owing to the intricate and multifaceted characteristics of OA, several therapeutic modalities exist, with the goal of achieving targeted disease management. Generally speaking, therapeutic substances disrupt the biochemical pathways that cartilage cells use to function .comprise immunological suppressants, cytokine inhibitors, proteolytic enzyme inhibitors (metalloproteinases, for example), antioxidants that stop oxidative stress, medications that stop chondrocyte hypertrophy and death, and, lastly, inhibitors of mediators that exacerbate the illness.(38)

Regenerative techniques can be used to treat osteoarthritis. Specifically, the platelet rich plasma (PRP) technique, which involves injecting the patient's own plasma into the arthritic joint to stimulate cartilage rebuilding. The elevated level of growth factors in by disrupting the inflammatory pathways, plasma promotes the production of cartilage matrix, bone regrowth, and pain alleviation. Hyaluronic acid (HA) injections combined with other medications may be a successful therapy for cartilage repair. HA is a viscoelastic lubricant that promotes the synthesis of proteoglycan and reduces inflammation. Additionally, HA increases its own synthesis, suggesting that a positive feedback mechanism is at work . The application of parathyroid hormone (PTH) to the proliferation of chondrocyte precursors.(39,40)

1) Topical NSAID Applications:

Currently, only a few medications are approved for the treatment of knee OA. First-line therapy for mild to moderate knee OA is the use of topical NSAIDs. In particular, ibuprofen is advised because to its relative safety, affordability, and clinical efficacy. Topical treatments have an advantage over oral prescriptions in that they bypass the first pass, or liver metabolism. It is possible to obtain higher local plasma concentrations with very small dosages.(41) To obtain the same local dose with oral prescriptions, a greater dosage resulting in a higher systemic exposure is required. Consequently, systemic responses, overdose, and drug-drug interactions are more likely to occur with oral administrations than with topical treatments, which are linked with side effects related to local skin reactions like itching or

rashes .As was previously mentioned, the mechanism of action for topical or oral treatments is that inflammatory processes directly cause pain in OA patients.(42)

2) Oral NSAIDs:

These are additional, previously authorised treatments for OA pain. As previously mentioned, they function by obstructing the COX-1 and/or COX-2 signalling pathway, which prevents prostaglandin formation and nociceptive transmission. (43)One benefit of oral administration is the ability to obtain larger plasma concentrations, which in turn leads to better relief of pain. The drawback is that the mechanisms of COX-1 and COX-2 play a significant role in renal perfusion and gastric protection in addition to inflammatory processes at the site of OA.(44,45)

Inhibition of these enzymes can cause a variety of adverse consequences, including renal hypoperfusion and stomach ulcers.(46) As a result, use should be restricted to the smallest dosage for the shortest amount of time .As a common over-the-counter NSAID, diclofenac or ibuprofen are currently used mostly.(47,48)

3) Intraarticular Corticosteroid Injections (IACI):

With their strong anti-inflammatory qualities, injections like triamcinolone acetonide influence the course of the illness in knee OA. Their method of action involves binding to glucocorticoid receptors on cartilage cells, which activates anti-inflammatory responses and causes the production of leukotriene, prostaglandins, arachidonicacid, lipocortin, and pro-inflammatory cytokines to be downregulated. Unfortunately, these beneficial benefits are very temporary; depending on the glucocorticoid given, effective pain reduction may only be achieved for 1 to 5 months.(49,50)

The two main issues with the usage of IACI are its short action interval and systemic adverse effects. Additionally, it is important to closely manage dosage and time intervals because several research have demonstrated that large dosages and prolonged exposure only result in harmful consequences.(51)

4) Intraarticular Hyaluronic Acid:

The suggested treatment strategy for knee OA does not yet include alternative methods for intraarticular drugs (IA), such as hyaluronic acid (HA) or platelet-rich plasma (PRP).High molecular weight glucosamines, such as HA, are produced by synoviocytes, chondrocytes,

and fibroblasts.(52) They provide synovial fluid its viscoelastic and lubricating properties, which shield cartilage from mechanical deterioration. Although defective synoviocyte synthesis and molecular fragmentation cause a reduction in the quantity and molecular weight of endogenous HA in the case of OA, the precise mechanism underlying symptom relief is yet unclear. (53)

Conclusion

It is thought that osteoarthritis is a complicated ailment that affects the entire joint. As a result, a thorough treatment plan should concentrate on several pathways and joint components at once. At this moment, therapy efforts have advanced to the point where we are able to successfully manage OA-related pain and suffering. But stopping the disease's development or finding a full recovery are still unattainable objectives.

It is imperative to intensify research efforts and target not just pain management but also disease modification and possibly curative techniques to improve the quality of life of afflicted individuals, given the rising incidence of OA in the ageing population. Since each patient has a unique clinical presentation, these tactics should be customised to their needs, taking into account the fact that different people experience OA in different ways.

This emphasises how crucial it is to look into treatment alternatives that cover the whole range of the illness, taking into account both the distinct symptoms of each patient's condition and the disease's varied presentations.

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